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Convenient Assembly of Privileged (Hetero)Arene-Fused Benzo[1.4]oxazepines via Two Tandem S_NAr Events. Part 2 – The Use of *o*-(*N*-(Hetero)aryl)aminomethyl phenols

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Abstract: As was anticipated based on mechanistic reasoning, bis-nucleophilic *o*-(arylamino)methyl phenols underwent a facile, base-promoted cyclocondensation with reactivity matched bis-electrophilic (hetero)aromatic substrates to give a rare type of substituted diarene-fused [1.4]oxazepines. The finding further supports the idea of the importance of the Smiles rearrangement in the interim of two S_NAr events ultimately leading to the formation of the central cycle in the newly formed tricylic scaffold.

Introduction

In the recent years, we have been developing a facile approach to constructing (hetero)arene-fused benzo[1.4]oxazepines **3** which involves a base-promoted cyclocondensation of reactivity matched bis-nucleophiles **1** and (hetero)aromatic bis-electrophiles **2** vicinally substituted with two leaving groups (LGs). The reaction is thought to proceed via two consecutive S_NAr steps intermitted by a Smiles rearrangement step. The latter have been shown to be essential for the completion of the ring-forming process: substrate pairs that are not capable of effectively undergoing said O→N (hetero)aryl group migration do not yield the anticipated [1.4]oxazepine product and the process stalls after the first S_NAr step.[1] The approach is rather universal for phenols substituted at the *ortho*-position with a nucleophilic 'Y-Z-H' motif which can be activated by deprotonation in the course of the reaction. So far, we have shown it to be applicable to the one-step synthesis of carba- and aza-versions of dibenzo[*b,f*][1,4]oxazepin-11(10*H*)-ones (**3a**),[2] dibenzo[*b,f*]pyrazolo[1,5-*d*][1,4]oxazepines (**3b**),[3] 2,3-dihydrodibenzo[*b,f*]imidazo[1,2-*d*][1,4]oxazepines (**3c**),[4] dibenzo[*b,f*][1,4,5]oxathiazepine 5,5-

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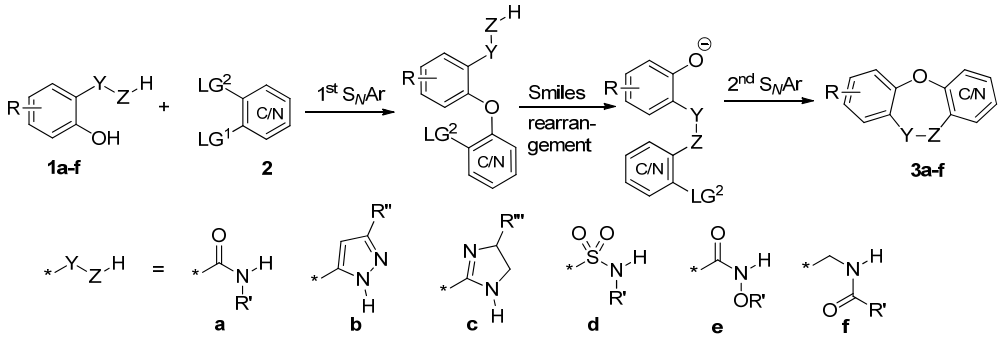
dioxides (**3d**),[5] 10-alkoxydibenzo[*b,f*][1,4]oxazepin-11(10*H*)-ones (**3e**),[6] and 10-carbonyl dibenzo[*b,f*][1,4]oxazepines (**3f**)[1] (Scheme 1).



Scheme 1. General synthetic approach to tricycles **3**.

The latter case (**1f→3f**) provided a particularly useful insight into the mechanistic requirements for the formation of the [1.4]oxazepine ring.[1] Unlike in other bis-nucleophiles **1a-e**, the phenolic hydroxyl group in **1f** is not stabilized by conjugation with an electron-withdrawing group. This raises the energy of phenoxide **7** and thus makes it energetically unfeasible for certain substrate pairs (those which do not sufficiently stabilize the postulated Meisenheimer intermediate **6**) to undergo the Smiles rearrangement after the initial S_NAr step. This led to the formation and isolation of diaryl ether **5** as the sole principal product of the reaction with such substrate pairs. Considering that we were able to restore the desired course of the ring-forming process toward **8** by introducing electron-withdrawing R group in substrates **1f** (thereby stabilizing **7** and rendering the Smiles rearrangement a thermodynamically feasible process), we pondered other means to drive it forward. It occurred to us that by increasing nucleophilicity of the nitrogen-atom in intermediate **4**, the Smiles rearrangement would become more kinetically favored. While some degree of delocalization of the negative charge in **4** is probably needed to enable formation of the latter, replacing the carbonyl substituent in **1f** with a (hetero)aromatic substituent (**9**) may serve the purpose and favor the Smiles rearrangement for those substrates **2** which previously did not yield [1.4]oxazepines **8** (Fig. 1). Herein, we present the outcome of testing this hypothesis.[7]

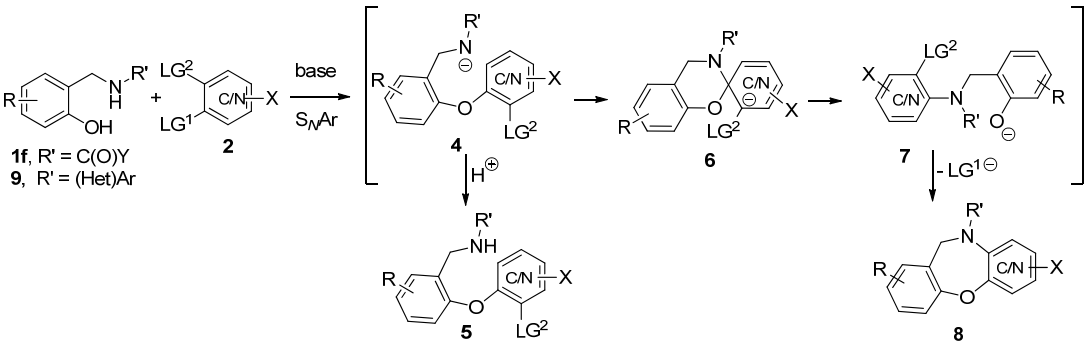


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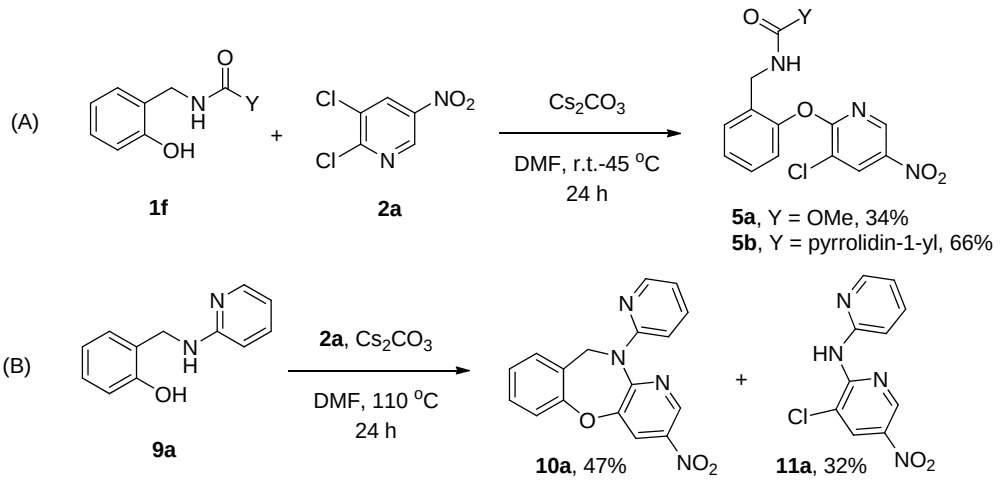
Fig. 1. Involvement of the previously explored (**1f**) and the newly investigated (**9**) bis-nucleophiles in cyclocondensation with reactivity-matched partners **2**.

Results and Discussion

For our initial experiments, we selected bis-electrophilic 2,3-dichloro-5-nitropyridine (**2a**) as it previously failed to deliver [1.4]benzoxazepine cyclocondensation products **8** with bis-nucleophiles **1f**. Instead, only respective diaryl ethers **5a-b** were obtained in modest yield attesting to the failure of the respective initial adduct **4** to go through the Smiles rearrangement barrier.[1] When we attempted involving **2a** in Cs_2CO_3-promoted reaction with **9a** (prepared, as all other phenol bis-nucleophiles employed in this work, via reductive amination of salicylic aldehyde with respective aromatic amine[8]), the full consumption of the starting materials was achieved in 24 h at 110 ºC and, to our delight, the anticipated product **10a** was obtained in 47% yield. In addition to [1.4]oxazepine **10a**, however, a substantial amount (32%) of non-cyclized product **11a** lacking the *o*-hydroxybenzyl moiety was isolated from the reaction mixture (Scheme 2).



Scheme 2. (A) The earlier observed reactions of **2a** with bis-nucleophiles **1f**[1] and (B) the recently obtained result from its reaction with **9a**.

Both products **10a** and **11a** presumably resulted from reactions involving the Smiles rearrangement. **10a** is the direct manifestation of the reactivity depicted in Fig. 1. **11a** cannot form in a direct S_NAr-type reaction with **9a** acting as an *N*-nucleophile (as we demonstrated in the control experiments discussed below). A feasible mechanism justifying the formation of **11a** is shown in Fig. 2. It involves the same steps as the formation of **10a** except for the last step where, instead of the second, ring-closing S_NAr event, the loss of *o*-hydroxybenzyl group (likely in the form of *o*-quinone methide) likely occurred.

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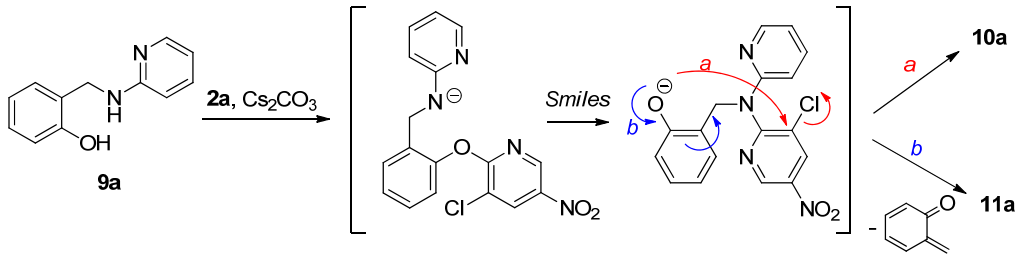
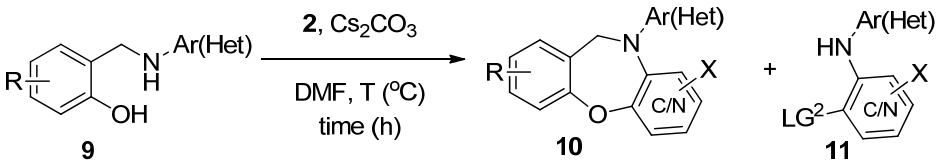
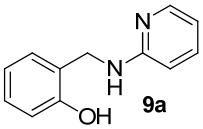
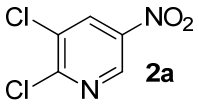
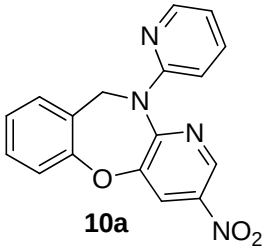
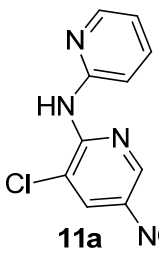


Fig. 2. Mechanistic rationale for the formation of products **10a** and **11a**.

Having established **9a** as a competent bis-nucleophile for condensation with bis-electrophilic (hetero)aromatic substrates **2a** capably of going through the Smiles rearrangement *en route* to [1.4]oxazepine **10a** (while also observing an unexpected complication in the formation of **11a**), we proceeded to screen a set of *o*-(arylamino)methyl phenols (**9a-d**) in reactions with bis-electrophilic (hetero)aromatic partners **2a-h** (Table 1). All reactions were run under essentially the same conditions; slight variations in temperature and reaction time were dictated by the need to drive reactions to completion (as monitored by analytical HPLC analysis of the reaction mixtures).

Table 1. Reactions of *o*-(arylamino)methyl phenols **9a-d** with bis-electrophilic (hetero)aromatic substrates **2a-h**.



Entry	**9**	**2**	Product **10(11)**	T (°C)	Time (h)	Yield (%)
1	 **9a**	 **2a**	 **10a**  **11a**	110	24	47 (**10a**); 32 (**11a**)

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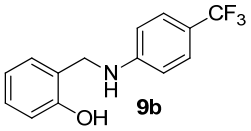
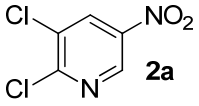
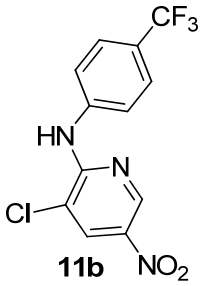
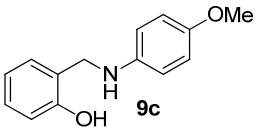
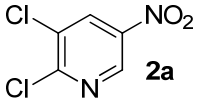
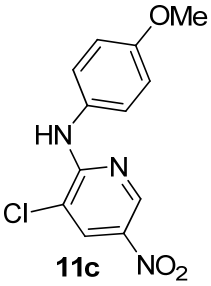
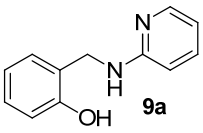
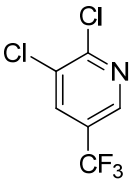
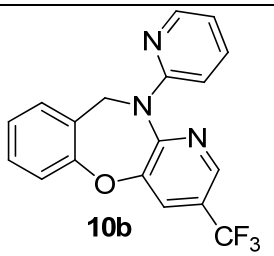
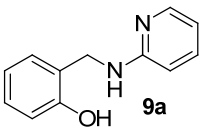
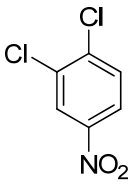
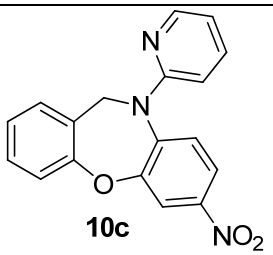
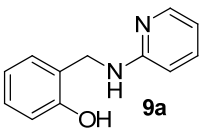
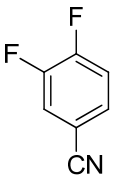
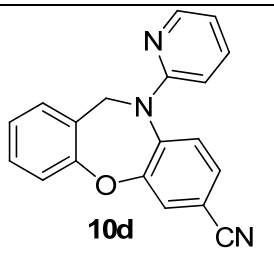
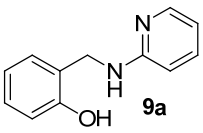
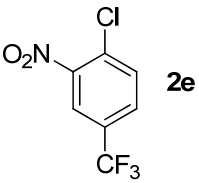
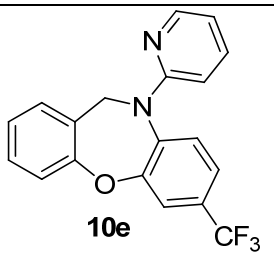
2	 **9b**	 **2a**	 **11b**	110	24	67
3	 **9c**	 **2a**	 **11c**	110	24	51
4	 **9a**	 **2b**	 **10b**	110	36	48
5	 **9a**	 **2c**	 **10c**	110	36	51
6	 **9a**	 **2d**	 **10d**	110	36	62
6	 **9a**	 **2e**	 **10e**	110	36	59

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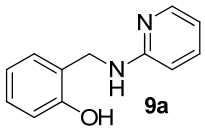
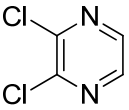
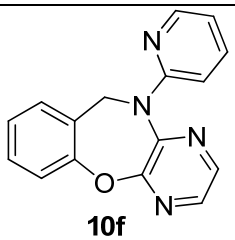
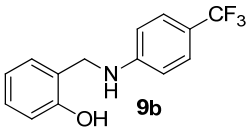
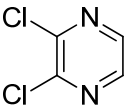
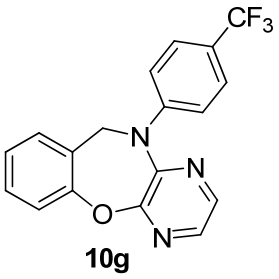
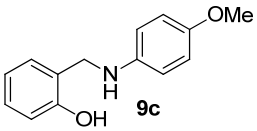
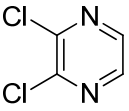
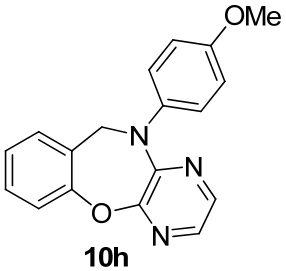
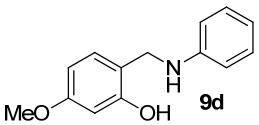
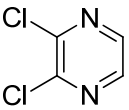
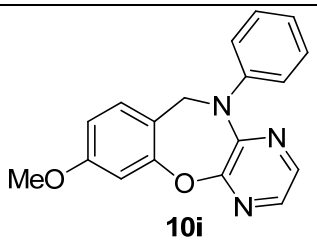
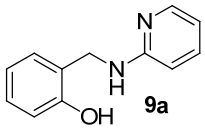
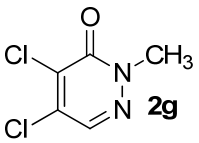
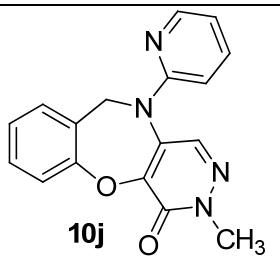
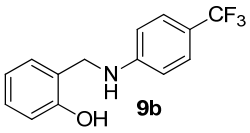
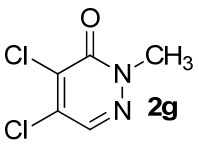
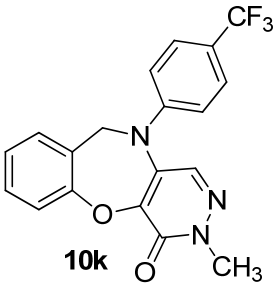
7	 **9a**	 **2f**	 **10f**	80	12	72
8	 **9b**	 **2f**	 **10g**	80	12	74
9	 **9c**	 **2f**	 **10h**	80	12	76
10	 **9d**	 **2f**	 **10i**	80	12	68
11	 **9a**	 **2g**	 **10j**	100	24	59
12	 **9b**	 **2g**	 **10k**	100	24	54

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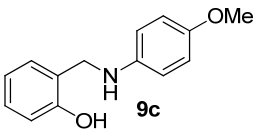
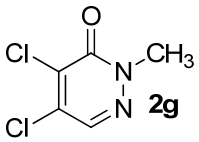
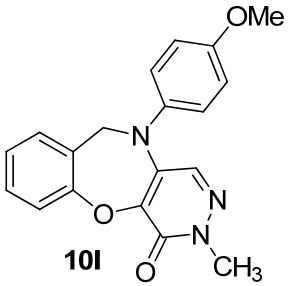
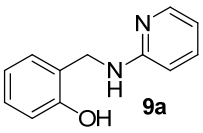
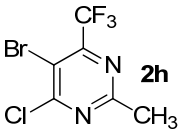
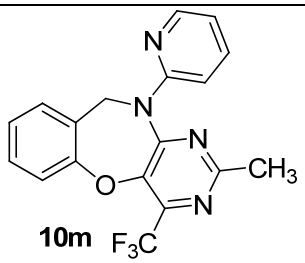
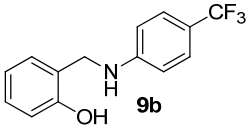
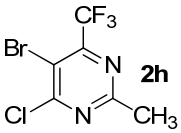
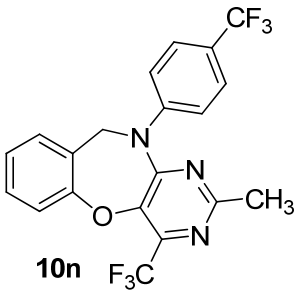
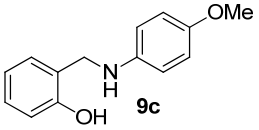
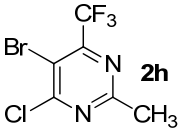
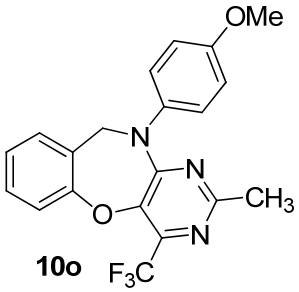
13	 **9c**	 **2g**	 **10l**	100	24	51
14	 **9a**	 **2h**	 **10m**	100	24	58
15	 **9b**	 **2h**	 **10n**	100	24	41
16	 **9c**	 **2h**	 **10o**	100	24	55

As it is evident from the data presented in Table 1, the unwanted *o*-quinone methide elimination leading to the formation (sometimes exclusive) of non-cyclized products **11** was substrate-specific and was observed only in reactions involving **2a** as the bis-electrophilic partner. In all other cases, the desired tricylic *N*-(hetero)aryl [1.4]diazepinones **10a-o** were obtained in fair to good yields. The regiochemical identity of these compounds, corresponding to the intermittent Smiles rearrangement, was unequivocally established, when possible, by the through-space interactions between neighboring protons in the NOESY spectra as shown in Fig. 3 for a set of representative compounds.

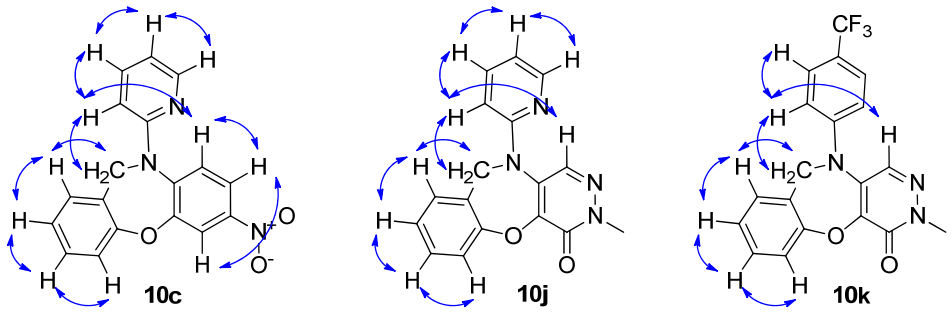
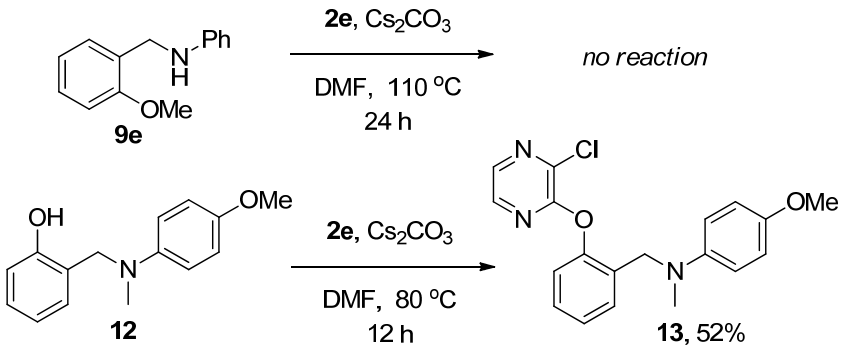


Fig. 3. Through-space interactions observed in the NOESY spectra of compouns **10c**, **10j** and **10k**.

The results presented in Table 1 also allow concluding that a number of substrates (**2a-e**), some of which were previously deemed unreactive towards weaker bis-nucleophiles **1f** (presumably, due to inability of the initial S_NAr products to cross the Smiles rearrangement barrier) were now found capable of delivering the target [1.4]oxazepines **10** via tandem S_NAr-Smiles rearrangement-S_NAr process.

In order to additionally confirm that compounds **11** cannot form *via* a direct S_NAr process involving bis-nucleophilic phenols as *N*-nucleophiles, we prepared and tested methoxy derivative **9e** in the reaction with **2f**. While this attempt delivered no product, the respective *N*-methyl derivative **12** gave phenoxy pyrazine product **13**, thereby confirming that the phenoxide anion is the one capable of bringing about S_NAr steps leading to the formation of products 10(11) (Scheme 3).



Scheme 3. Results of control experiments with *O*- and *N*-substituted compounds **9e** and **12**.

It should be noted that compounds **10a-o** reported in this work are representatives of an exceedingly rare type of substituted diarene-fused [1.4]oxazepines substituted with a (hetero)aryl group at the ring nitrogen atom. Although they clearly belong to the general cluster of privileged tricyclic scaffolds,[1] these compounds have not been subject of extensive biological annotation

(perhaps due to the lack of streamlined methods to construct them), except for some examples of histone deacetylase inhibitors[9] and compounds endowed with hyperthermal activity.[10]

Conclusions

In summary, by using mechanistic reasoning we designed a series of structurally simple bis-nucleophilic phenols having greater nucleophilicity compared to previously studied versions of these substrates. These gave rise to a rare type of substituted tricyclic [1.4]oxazepines in base-promoted cyclocondensation reaction with reactivity-matched bis-electrophilic aromatic partners. The scope of the reaction is markedly broader with respect to the latter. The study further supports the hypothesis about the Smiles rearrangement occurring in these reactions in the interim of two S_NAr events as a pre-requisite to a successful formation of [1.4]oxazepine ring.

Experimental Section

General procedure for preparation of compounds 10a-o and 11a-c. A mixture of aminophenol **9a-c** (0.5 mmol), bis-electrophilic (hetero)aromatic substrates (0.5 mmol) and freshly calcinated Cs_2CO_3 (490 mg, 1.5 mmol) in anhydrous DMF (2 mL) was stirred, at a given temperature for 12 h. DMF was removed *in vacuo* and the residue was treated with water (10 mL), which caused a viscous oil to separate. It was extracted with CH_2Cl_2 (5 mL), the organic layer was separated, dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel using an appropriate gradient of ethyl acetate in hexanes as eluent.

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Keywords: nucleophilic aromatic substitution; Smiles rearrangement; [1.4]oxazepines; privileged structures; reactivity-matched synthons

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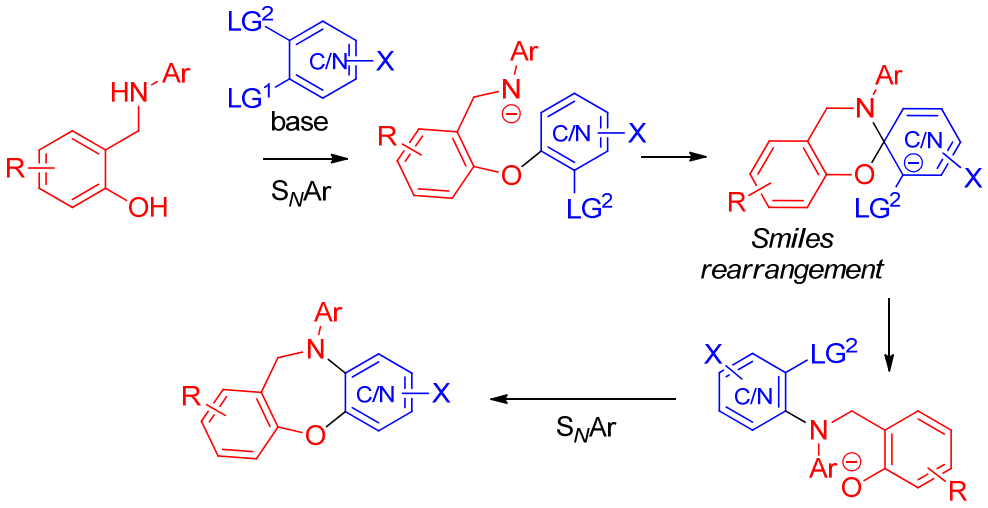
Graphical Abstract:



TOC text:

Simple bis-nucleohilic *o*-[(hetero)arylamino]methyl phenols are more reactive than the earlier studied acyl versions in the formation of [1.4]oxazepine cycle via double nucleophilic substitution. The resulting structurally new *N*-(hetero)aryl [1.4]oxazepines formed in good yield. This finding supports the idea of the importance of the Smiles rearrangements in between of the two S_NAr events.

Key topic:

Heterocycle synthesis